A phase II investigator-initiated frontline trial of evorpacept (ALX148), lenalidomide and rituximab for high tumor burden indolent B-cell non-Hodgkin lymphoma

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Abstract

Introduction. We have recently completed a phase I trial of evorpacept (formerly known as ALX148), a novel high-affinity signal regulatory protein (SIRPα fusion protein that blocks cluster of differentiation (CD)47, in combination with lenalidomide and rituximab (R2) in patients with relapsed refractory indolent B-cell non-Hodgkin lymphoma (iNHL). The combination was safe, no dose limiting toxicity was observed at a dose of 60 mg/Kg on day (D) 1 of a 28-day cycle, and more than 80% of patients experienced a complete response (CR). We present here a phase 2 study investigating the efficacy of this regimen in patients with previously untreated and high tumor burden iNHL.

Methods. This single arm phase II study (NCT05025800) was conducted between January and November 2024 (data cut-off 07/2025). Adult patients with previously untreated and advanced stage iNHL, who met indication for treatment according to The Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria were included. Evorpacept was administered intravenously (IV), in a 28-day cycle, for 6 cycles, at the recommended phase 2 dose of 60 mg/Kg on D1; rituximab IV was given weekly during cycle 1, and on D1 during cycles 2-6; lenalidomide was given orally on D1-21 during cycles 1-6. Toxicity was evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) version 5. The primary endpoint was best CR rate per Lugano 2014 criteria.

Results. Twenty-four patients were included in the study, and all were evaluable for safety and efficacy. Median age was 64 (33-76) and 13 (54%) were male; 14 (58%) had follicular lymphoma, including 5 patients with grade 3A, and 10 (42%) had marginal zone lymphoma (MZL), including 4 with extra-nodal, 4 with nodal, and 2 with splenic subtype; median largest lymph node size was 3.6 cm (range, 1.5-7.5 cm), median maximum standardized uptake volume was 7.1 (range, 3-32), and all patients had intermediate-high Follicular Lymphoma International Prognostic Index (FLIPI). Median number of cycles was 6 (range, 3-6), and all patients had completed treatment at time of data cut-off. The most common (> 1 patient) grade 3-4 adverse events included: neutropenia (29%), all resolved with growth factor, infections (12.5%), alanine transferase (ALT) increase (12.5%), aspartate transferase (AST) increase (12.5%), and infusion related reaction (8%). Ten (42%) patients required a dose reduction in lenalidomide, mainly due to infections, but none in evorpacept; 2 (8%) patients discontinued lenalidomide and 1 (4%) evorpacept, due to AST/ALT elevation. Twenty-two (92%) patients achieved CR, 2 (8%) partial response, and overall response rate was 100%. After a median follow-up of 10 months (95% confidence interval, 9-12 months), 2 patients have progressed (1 with likely baseline transformed MZL), with a 1-year progression-free survival rate of 87%. At most recent follow-up no patients have died, and 1-year overall survival rate was 100%.

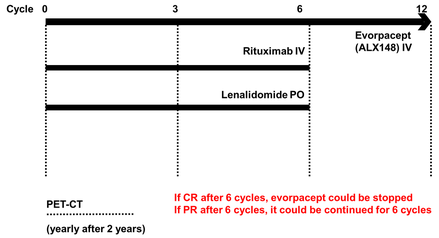
Conclusions. The addition of evorpacept to R2 is a safe and effective frontline non-chemotherapy regimen for iNHL patients, resulting in high CR rates. While longer follow-up matures, serial blood samples are being evaluated for circulating tumor DNA by phased variant enrichment and detection

Background

- Signal regulatory protein (SIRPα)+ macrophages are increased at time of progression after lenalidomide and rituximab (R^2) in patients with relapsed refractory indolent B-cell non-Hodgkin lymphoma (iNHL).
- Evorpacept (former ALX148) is a novel high affinity CD47 blocker that abrogates the 'do-not-eat-me signal' provided to SIRPα+ macrophages, without targeting red blood cells. In addition, it increases antibody-dependent cellular phagocytosis when combined with monoclonal antibodies.
- In a phase I trial including patients with relapsed refractory iNHL, its combination with R^2 was safe, no dose limiting toxicity was observed at an evorpacept dose of 60 mg/Kg on day (D) 1 of a 28-day cycle, and more than 80% of patients experienced a complete response (CR).

Methods

- This single arm phase II study (NCT05025800) was conducted between January and November 2024 (data cut-off 07/2025).
- Adult patients with previously untreated and advanced stage iNHL, who met indication for treatment according to GELF criteria were included.
- Evorpacept was administered intravenously (IV), in a 28-day cycle, for 6 cycles, at the RP2D of 60 mg/Kg on D1; rituximab 375 mg/m^2 IV was given weekly during cycle 1, and on D1 during cycles 2-6; lenalidomide 20 mg PO was given on D1-21 during cycles 1-6.
- Toxicity was evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) version 5. The primary endpoint was best CR rate per Lugano 2014 criteria.



Baseline characteristics

Patients (N=24)	Number (%); Median [Range]
Age	64 [33-76]
Caucasian	23 (96)
Female	11 (46)
Hemoglobin (g/dL)	13.4 [9.6-15.7]
β2-microglobulin (mg/L)	2.5 [1.5-7.2]
LDH (U/L)	204 [150-777]
Follicular lymphoma	14 (58)
Marginal zone lymphoma	10 (42)
Bone marrow, involved	12 (50)
B-symptoms, present	5 (21)
Ann Arbor Stage IV	21 (87.5)
Involved nodal areas (n)	5 [0-7]
Largest lymph node (cm)	3.6 [1.5-7.5]
SUV_{max}	7.1 [3-32]
FLIPI score, high	13 (54)
FLIPI-2 score, high	9 (37.5)
PRIMA PI, high	10 (42)

Safety and tolerability

Patients (N=24)	Grade 1-2	Grade 3-4
Neutropenia	12 (50)	7 (29)*
ALT increase	13 (54)	3 (12.5)
AST increase	12 (50)	3 (12.5)
Infection	8 (32)	3 (12.5)
Infusion related reaction	8 (32)	2 (8)
Thrombocytopenia	7 (29)	1 (4)
Skin rash	7 (29)	1 (4)
Bilirubin increase	2 (8)	1 (4)
Fatigue	15 (62.5)	0 (0)
Anemia	8 (32)	0 (0)
Creatinine increase	7 (29)	0 (0)
Constipation	5 (21)	0 (0)
Headache	5 (21)	0 (0)
Insomnia	4 (16)	0 (0)
Muscle cramps	4 (16)	0 (0)
Diarrhea	4 (16)	0 (0)
Xerophthalmia	2 (8)	0 (0)
Hypercalcemia	2 (8)	0 (0)
Hyperkalemia	2 (8)	0 (0)
Peripheral sensory neuropathy	2 (8)	0 (0)
Anorexia	2 (8)	0 (0)
Arthralgia	2 (8)	0 (0)
Atrial fibrillation	1 (4)	0 (0)

- * GCSF used for all

Dose adherence

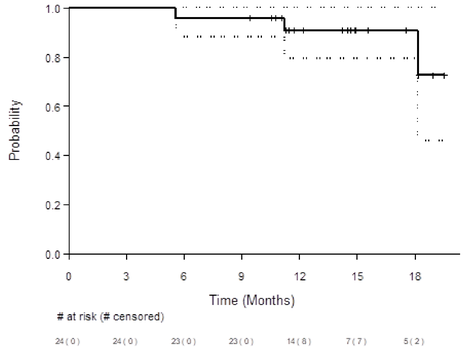
Patients (N=24)	Number (%); Median [Range]
Cycles (n)	6 [3-6]
Lenalidomide dose reduction	10 (42)*
Lenalidomide delay	16 (67)*
Lenalidomide discontinuation	2 (8)**
Evorpacept dose reduction	0 (0)
Evorpacept delay	8* (33)
Evorpacept discontinuation	1 (4)**

- *: mainly due to infection, independent of attribution
- **: due to elevated LFTs, independent of attribution

Response to Therapy

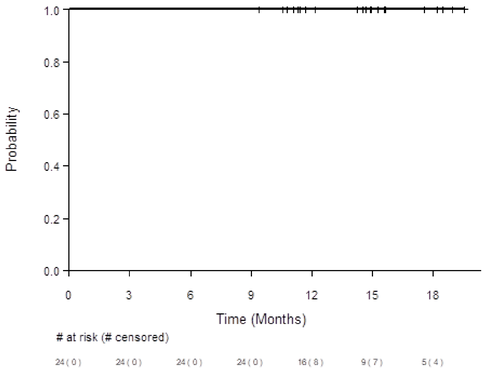
- ORR was 100% at all timepoints
- Primary endpoint (CR rate of 80%, compared to historical 50%, was met; power 80%, 2-sided α-error 0.05)

Progression-free survival



- After a median follow-up of 15 months (95% confidence interval, 12-16 months), 3 patients have progressed (1 with likely baseline transformed MZL), with a 1-year progression-free survival rate of 91%.

Overall Survival



- At most recent follow-up no patients have died, and 1-year overall survival rate was 100%.

Conclusions

- The addition of evorpacept to R^2 is a safe and effective frontline non-chemotherapy regimen for iNHL patients, resulting in high CR rates.
- While longer follow-up matures, serial blood samples are being evaluated for circulating tumor DNA by phased variant enrichment and detection sequencing (PhasED-seq) to determine the minimal residual disease eradication rate with this novel regimen.

Acknowledgements

- PS salary is supported by the Leukemia Lymphoma Society (now BCU) Career Development Program
- The study was supported by ALX Oncology

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